12 An introduction to metabolic disorders

Individual inborn or congenital errors of metabolism are very rare. However, more than 1400 inherited metabolic diseases have been described. Many of these disorders are potentially treatable via diet and/or drug therapy. It is essential that a rapid accurate diagnosis be made to ensure rational treatment, correct genetic advice and future antenatal diagnosis.

The complexity, diversity and rarity of congenital errors of metabolism in children are potential barriers to comprehensive care. Pharmacists have a key role in the care of these children. Traditionally, the pharmacist's role has focused on the supply of medication, including unlicensed or orphan products and chemicals obtained from non-pharmaceutical suppliers. However, pharmacists may also be involved in:

- **creating care plans and emergency protocols**
- **routine clinical pharmacy activities**
- **liaising with children/carers.**

Objectives

On completion of this chapter you will be able to:

- **describe some presenting features of inborn errors of metabolism**
- **outline the main metabolic pathways and possible defects**
- **give some examples of inborn errors of metabolism**
- **describe some treatment options, including their availability and status**
- **describe the pharmaceutical challenges in caring for this complex, diverse patient group from both a community and hospital pharmacy perspective.**

1. The disease

Metabolic pathways

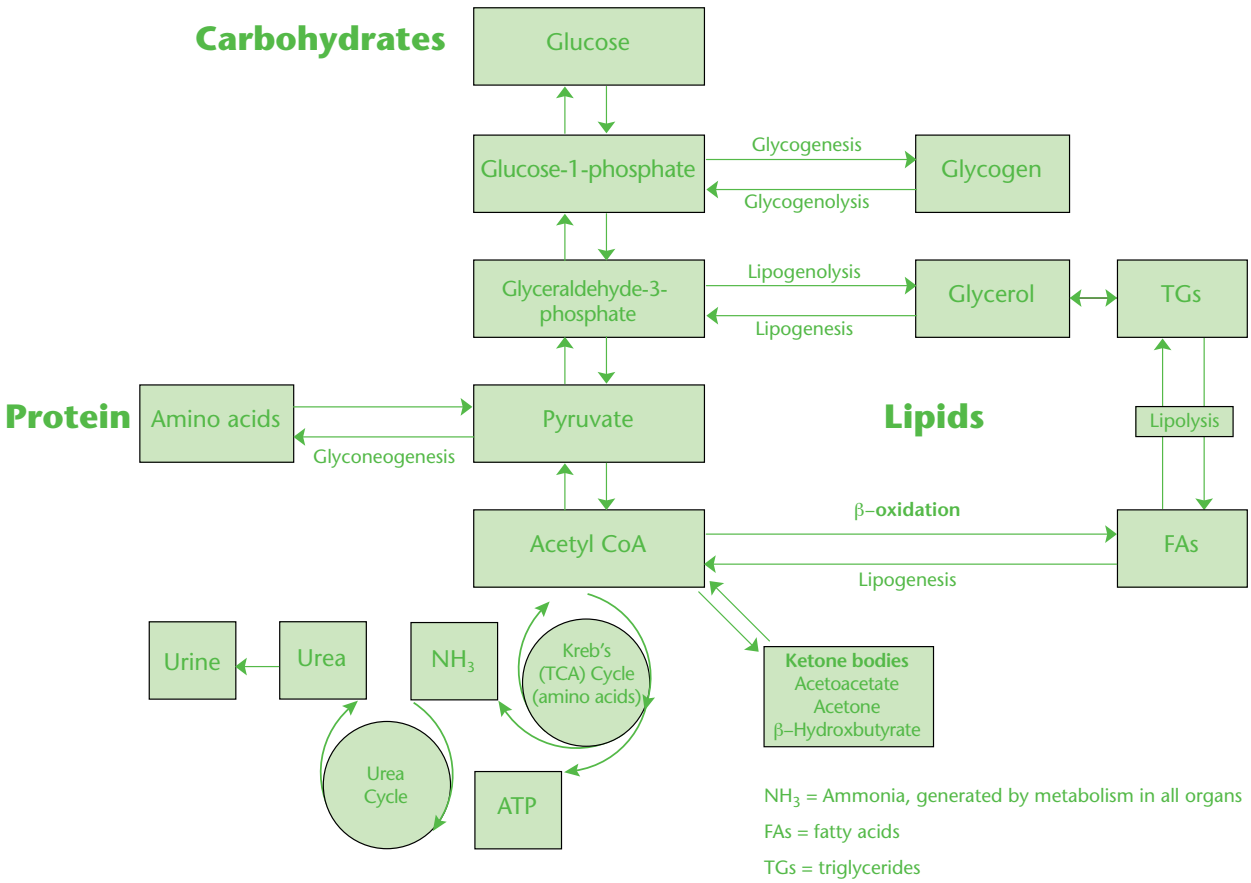
The term metabolism refers to all biochemical processes and pathways in the body. Enzymes play a key role in many of these processes and changes in their function, as a result, of genetic mutation can lead to problems in these pathways.

The major metabolic pathways for proteins, carbohydrates and lipids are closely integrated with key molecules, such as acetyl co-enzyme A via complex mechanisms (see figure below). A genetic defect in any part of the major metabolic pathways is known as an inborn or congenital (if present from birth) error of metabolism.

Inborn errors of metabolism can be divided into three pathophysiological diagnostic groups:

- **Disorders that disrupt the synthesis or catabolism† of complex molecules with symptoms that are permanent, progressive, independent of intercurrent events and not related to food intake. These include lysosomal disorders†, peroxisomal disorders† and disorders of intracellular transport and processing.**
- **Disorders that lead to an acute or progressive accumulation of toxic compounds as a result of metabolic block. These include disorders of amino acid metabolism (phenylketonuria†, homocystinuria†, maple syrup urine disease), organic acidurias, congenital urea cycle defects and sugar intolerances (galactosaemia).**
- **Disorders with symptoms due to a deficiency of energy production or utilisation within the liver, myocardium, muscle or brain. These include congenital lactic acidemias, fatty acid oxidation defects, gluconeogenesis† defects and mitochondrial respiratory chain disorders.**

Metabolic Pathways



1.1 Incidence and prevalence

The majority of inborn errors of metabolism are inherited by autosomal recessive genetics.

As a result, the individual incidence of metabolic disorders can vary depending on the ethnic origin of the local population. Overall incidence of individual inborn errors of metabolism can range as follows:

- **very rare (e.g. maple syrup urine disease 1:250,000; homocystinuira 1:250,000)**
- **extremely rare (1:1,000,000)**
- **relatively more common but still rare (e.g. phenylketonuria† 1:6,000-10,000;**
- **galactosaemia 1:60,000).**

However, if there are more than 1000 inherited metabolic disorders overall, each occurring at the rate of one in a million, this means that one in 1000 people will be affected and one in 500 will be a carrier. It is therefore likely that every community pharmacist will come into contact with patients with inherited metabolic disorders, often unknowingly.

2. Signs and symptoms

Metabolic disorders can present with a great diversity of signs and symptoms that mimic non-genetic disorders. Common presenting symptoms are:

- **acute neonatal symptoms (described below)**
- **failure to thrive**
- **CNS symptoms such as developmental delay, movement or psychiatric disorder or cerebral palsy**
- **sudden infant death syndrome (SIDS)**
- **episodic illness – anorexia, vomiting, lethargy, coma**
- **cardiomyopathy**
- **muscular – hypotonic, weakness, cramps**
- **gastrointestinal – anorexia, vomiting, diarrhoea, malabsorption**
- **liver disease**
- **ophthalmic abnormalities**
- **Reye's syndrome-like illness**
- **dysmorphic features**
- **metabolic – acidosis, hypoglycaemia.**

Clinical categories

With the exception of systematic neonatal population screening (for phenylketonuria† and galactosaemia) or screening in 'at-risk' families, a 'metabolic screen' is frequently performed on blood or urine of suspected cases as a differential diagnosis.

There are four categories of clinical circumstances that metabolic disorders can present:

- **Acute symptoms in the neonatal period**
  Babies have limited responses to severe illness with non-specific symptoms such as respiratory distress, hypotonia, poor sucking reflex, vomiting, diarrhoea, dehydration, lethargy and seizures. These can easily be attributed to other causes, such as infection.

  Babies with metabolic disorders of accumulation show deterioration after a normal initial period of hours to weeks.

- **Late-onset acute and recurrent symptoms**
  One third of children with metabolic disorders of toxic accumulation or energy production are late onset. The symptom free period is often over one year and may extend into late childhood, adolescence or even adulthood. Symptoms may be precipitated by minor viral infection, fever or severe diarrhoea which result in the body reverting to the breakdown of stored protein within the cells and tissue. This is known as decompensation. Sometimes these symptoms can also be precipitated by a sudden increase in the amount of protein eaten, for example, while on holiday or following a celebration.

  Children may improve spontaneously without intervention or require intensive care. They may appear normal between attacks.

- **Chronic and progressive general symptoms**
  Many apparently delayed onset presentations of metabolic disorders may be preceded by insidious symptoms such as gastrointestinal, neurological and muscular complaints.
- **Specific and permanent symptoms may reveal or accompany metabolic disorders**
  Some symptoms are distinctive but rare (lens discolouration and thromboembolic events in homocystinuria†), others are non-specific and common (hepatomegaly†, seizures, mental retardation).

  A number of symptoms may give rise to the diagnosis of a syndrome (e.g. Leigh's disease†) but may be caused by different metabolic disorders.

Activity 12.1

Look up the signs and symptoms of Leigh's disease† on the website of NORD – the National Organization for Rare Disorders or the European Union sponsored Orpha.net (http://www.rarediseases.org or http://www.orpha.net – To access the paper please go to www.nes.scot.nhs.uk/pharmacy/paediatrics/start.pdf and click on 'Activity Links'). Go to the 'Index of rare diseases' and scroll down.

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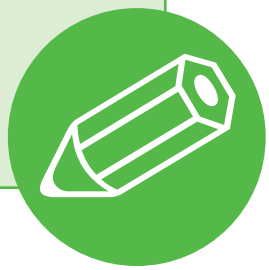

3. Management

The main aims of managing metabolic disorders through therapy are:

- **induce activity, as in the vitamin-responsive disorders**
- **counteract the biochemical disturbance and prevent acute intercurrent decompensation**
- **prevent chronic and progressive deterioration by diet and/or drug therapy.**

Approximately 12% of inborn errors of metabolism can be significantly controlled by therapy. In a further 55%, treatment is beneficial but in the remaining 33%, treatment has little effect.

3.1 Emergency treatment

Children can be suspected of having acute symptoms of a neonatal or late-onset metabolic disorder due to accumulation of toxic compounds as a result of metabolic block or deficiency of energy production. They require prompt simultaneous diagnosis, clinical and biochemical monitoring and emergency treatment.

Treatment is focused around supportive care and, once a diagnosis is established, directed towards the suppression of the production of toxic metabolites and stimulation of their elimination. Supportive care may involve:

- **ventilatory and circulatory support, particularly in very ill babies**
- **correction of electrolyte imbalance**
- **rehydration and maintenance hydration to counter poor feeding, increased renal fluid loss and to ensure efficient diuresis of toxic metabolites**
- **correction of acidosis, although mild acidosis can be protective against hyperammonaemia in urea cycle defects.**

More specific therapeutic approaches involve:

- **Nutrition – a hypercalorific nutritional intake of glucose is often required to prevent further protein and fat catabolism[†]. This is preferably administered enterally or, if the child is vomiting, from intravenous fluids or parenteral nutrition (especially in babies). Once toxic metabolites have normalised, appropriate long-term dietary treatment can be initiated.**
- **Exogenous toxin removal – peritoneal dialysis, haemofiltration or haemodialysis can be effective in removing toxic metabolites, such as ammonia in urea cycle defects.**
- **Vitamins – mega-doses of specific vitamins can act as cofactors to induce metabolism in various metabolic disorders (see table below)**

Cofactor	Metabolic disorder
Thiamine	Maple syrup urine disease (MSUD)
	Hyperlactataemia (pyruvate dehydrogenase disorders)
Biotin	Propionic aciduria
	Multiple carboxylase deficiency
Hydroxocobalamin	Methylmalonic aciduria
Riboflavin	Glutaric aciduria
	ß-oxidation defects
Carnitine	Branched-chain organic acidaemia
	Dicarboxylic acidaemia
	Primary hyperammonaemia

Note: Some texts refer to acidurias as acidaemias

- **Stimulation of an alternative pathway – depends on defect of metabolic pathway (see the table below).**

Drug	Condition	
Carnitine	In acute medium chain acyl CoA dehydrogenase deficiency (MCAD) crisis.	(See section 4.3 on page 159.)
Sodium benzoate, sodium phenylbutyrate	Hyperammonaemia in urea cycle defects.	(See Section 4.4 on Phenylbutyrate, carglumic acid page 161.)

3.2 Long-term treatment

Once emergency treatment has normalised or stabilised the acute metabolic defect, or has prevented deterioration in chronic and progressive metabolic disorders, appropriate long-term dietary and/or drug therapy can be initiated. An understanding of the metabolic pathways involved and the enzymes that are deficient has led to a number of developments to be made to replace these enzymes. Recombinant DNA technology has allowed the long term enzyme replacement in a number of lysosomal storage diseases.

The table overleaf lists examples of a number of metabolic disorders and the suggested drug therapy.

Metabolic disorder	Suggested drug therapy
Urea cycle disorders	
N-acetyl glutamate synthetase (NAGS) deficiency	Carglumic acid (Carbaglu®)
Carbamylphosphate synthase deficiency	Arginine Citrulline Carglumic acid Sodium benzoate Sodium phenylbutyrate
Ornithine carbamyl transferase deficiency	Arginine Citrulline Sodium benzoate Sodium phenylbutyrate
Arginosuccinic aciduria, Citrullinaemia	Arginine Sodium benzoate Sodium phenylbutyrate
Arginase deficiency	Sodium phenylbutyrate Sodium benzoate
Amino acid disorders	
Non-ketotic hyperglycinaemia	Sodium benzoate L-tryptophan Dextromethorphan Ketamine
Tyrosinaemia (Type I)	NTBC (2-[2 nitro-4 trifluoro-methylbenzoyl]-1,3, -cyclohexanedione)
Maple syrup urine disease	Thiamine
Organic acidaemias	
Isovaleric acidaemia	Carnitine Glycine
Methylmalonic acidaemia	Hydroxocobalamin Carnitine
Propionic acidaemia	Carnitine
Glutaric aciduria type I	Carnitine
Glutaric acidaemia type I & II	Riboflavin

Mitochondrial disorders	
Carboxylase defects	Biotin
Mitochondrial myopathies	Ubiquinone
Lactic acidosis (pyruvate dehydrogenase complex defects)	Dichloroacetic acid (dichloroacetate)
Congenital lactic acidosis	Riboflavin Thiamine
Mitochondrial respiratory chain defects	Thiamine
Lysosomal storage disorders	
Cystinosis	Mercaptamine (cysteamine)
Gaucher's disease	Imiglucerase Alglucerase Miglustat
Fabry disease	Agalsidase alpha and algasidase beta
Pompe's disease	Alglucosidase
Mucopolysaccharoidosis I	Laronidase
Mucopolysaccharoidosis II	Idursulfase
Mucopolysaccharoidosis VI	Galsulfase
Miscellaneous	
Homocystinuria†	Betaine Pyridoxine Hydroxocobalamin Folinic acid

Many products are not available in a suitable formulation for administration and may have an unpleasant taste or odour. This can pose some basic pharmaceutical challenges to community and hospital pharmacists.

The use of unlicensed medicines in paediatrics is well established and is often unavoidable in the management of inborn errors of metabolism. This is often as a result of a lack of robust evidence of efficacy due to small patient numbers. The use of unlicensed medicines is discussed in Chapter 2 – Medication and its forms on page 13. The table below lists examples of the availability and licensed status of some commonly used agents for metabolic disorders:

Form	Licensed Status	Availability*
Arginine		
Powder	Borderline substance for urea cycle disorders	Scientific Hospital Supplies
Tablet	Unlicensed pharmaceutical special	Special Products Ltd
Injection	Unlicensed pharmaceutical special	Martindale Pharmaceuticals
Oral solution	Unlicensed extemporaneously dispensed	
Biotin		
Tablet/injection	Unlicensed import	John Bell & Croyden
Carglumic Acid		
Dispersible tablet	Licensed	Orphan Europe (UK) (Carbaglu)
Carmitine		
Injection	Licensed all ages & indications	sigma-tau Pharma Limited UK (Carnitor)
30% oral solution	Licensed all ages & indications	sigma-tau Pharma Limited UK (Carnitor)
1g in 10ml oral solution	Licensed >12 years	sigma-tau Pharma Limited UK (Carnitor))
Chewable tablet	Unlicensed import	IDIS World Medicines
Riboflavin		
Tablet/injection	Unlicensed import	IDIS World Medicines
Sodium benzoate		
Injection/capsule/ oral liquid	Unlicensed pharmaceutical special	Martindale Pharmaceuticals
Tablet/powder	Unlicensed pharmaceutical special	Special Products Ltd
Sodium phenylbutyrate		
Injection	Unlicensed pharmaceutical special	Martindale Pharmaceuticals
Granules/tablet	Licensed all ages and indications	Swedish Orphan International (Ammonapps)
Thiamine		
Tablet	Formulations are licensed but indications are not	Non-proprietary via wholesaler
Injection	Unlicensed import	John Bell & Croydon
Ubiquinone (Coenzyme Q10)		
Capsules	Non-pharmaceutical dietary supplement	Lamberts Healthcare, Pharma-Nord
Oral solution	Unlicensed import	IDIS World Medicines

*Note: The sources quoted here may not be the only suppliers of these products.

4. Specific inborn errors of metabolism

In this section four examples of inborn errors of metabolism are discussed. The first two (phenylketonuria† and galactosaemia) are managed by diet therapy alone. They can also give rise to pharmaceutical challenges for the pharmacist when medicines are required.

The next two (MCAD deficiency and urea cycle disorders) are examples of inborn errors of metabolism where dietary management and medicines are required.

4.1 Phenylketonuria

Patients with phenylketonuria† (PKU) are unable to convert phenylalanine to tyrosine in the liver due to a recessively inherited defect in the enzyme phenylalanine hydroxylase.

The incidence of PKU is about 1:6,000-10,000.

If untreated, it may give rise to:

- **infantile spasms**
- **significant developmental delay with disturbed behaviour, hyperactivity and destructiveness in older children.**

PKU can be managed by dietary restriction of phenylalanine containing foods. Dieticians will normally provide advice and support for this. However, care must also be taken to avoid the sweetener aspartame (L-aspartylphenylalanine) that is contained in many paediatric medicine formulations as an alternative to sucrose. Therefore, the pharmacist must be aware of medication excipients and advise on appropriate formulations or choice of therapy.

Activity 12.2

Mrs P presents a prescription for co-amoxiclav suspension for her 5 year old daughter who has a chest infection. She asks you to check the ingredients as her daughter has 'PKU'.

a What is PKU?

b What excipients should be avoided in PKU?

c What would you recommend?

Check your dispensary stocks and list which liquid medicines contain aspartame.

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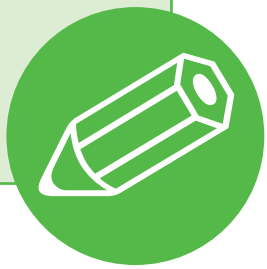

4.2 Galactosaemia

Patients with galactosaemia are unable to metabolise galactose, most frequently due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase. The incidence is about 1:60,000. Symptoms usually start within days of birth on the initiation of milk feeds.

Untreated infants can present with:

- **vomiting and diarrhoea**
- **failure to thrive**
- **jaundice**
- **liver dysfunction with hepatomegaly†**
- **hypoglycaemia**
- **abnormal clotting**
- **mental retardation**
- **cataracts.**

Treatment of severe cases involves total elimination of dietary galactose. The main source of dietary galactose is the disaccharide lactose (glucose and galactose), the predominant carbohydrate in milk and most milk-based infant formulae. Medications that contain lactose must also be excluded. Once again, the pharmacist must be aware of medication excipients and be able to advise on appropriate formulations or choice of therapy.

Activity 12.3

Can children with galactosaemia have medicines that contain sucrose? Give a reason for your answer.

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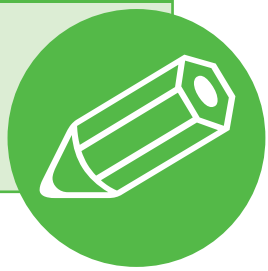


4.3 Medium chain acyl CoA dehydrogenase deficiency

Medium chain acyl CoA dehydrogenase (MCAD) deficiency is the most common inborn error of metabolism of fatty acid oxidation with an estimated incidence of 1:10,000. Lipid metabolism is important in maintaining energy homeostasis during fasting periods. When lipids (triglycerides) are to be oxidised by the body for energy they are first converted by lipolysis to fatty acids. These are oxidised by the ß-oxidation pathway and it is this pathway that is defective in MCAD deficiency.

Affected individuals appear normal until an episode of illness is provoked by an excessive period of fasting, usually due to an infection. The first presentation is usually between three months and two years. MCAD deficiency is the cause of 1-3% of sudden infant death syndrome in the most severe presentation.

Typical signs and symptoms include:

- **recurrent hypoketotic hypoglycaemia†**
- **Reye's syndrome-like illness (vomiting, lethargy, delirium, coma and convulsions)**
- **liver dysfunction.**

Accumulated medium chain acyl CoA esters bind to carnitine and are excreted in urine. This can lead to secondary carnitine deficiency† with muscle weakness or hypotonia. Treatment involves administration of enteral or intravenous glucose, depending on severity, to correct hypoglycaemia and provide energy, thereby removing the need to utilise fat. Carnitine can also be administered during a crisis to treat secondary carnitine deficiency and to promote excretion of excess esters. The mainstay of treatment is to avoid prolonged periods of fasting and treat signs of hypoglycaemia early. Attacks become less frequent during childhood as fasting tolerance improves with increasing body mass.

4.4 Urea cycle disorders

The urea cycle detoxifies ammonia and removes surplus amino group nitrogen from the body. About 80% of excreted nitrogen is in the form of urea, produced in the liver. The urea cycle involves five enzymes and an inherited defect can occur in each, characterised by hyperammonaemia.

Early symptoms of hyperammonaemia are non-specific and include:

- **lethargy**
- **hypothermia**
- **apnoea**
- **convulsions.**

Encephalopathy† can also develop.

Patients may present at any age but are more likely to develop symptoms during periods of metabolic stress such as infection precipitating protein catabolism†. Onset is most likely during the neonatal period, late infancy and puberty. In between episodes, patients are usually relatively well, although some may continue to have poor developmental progress.

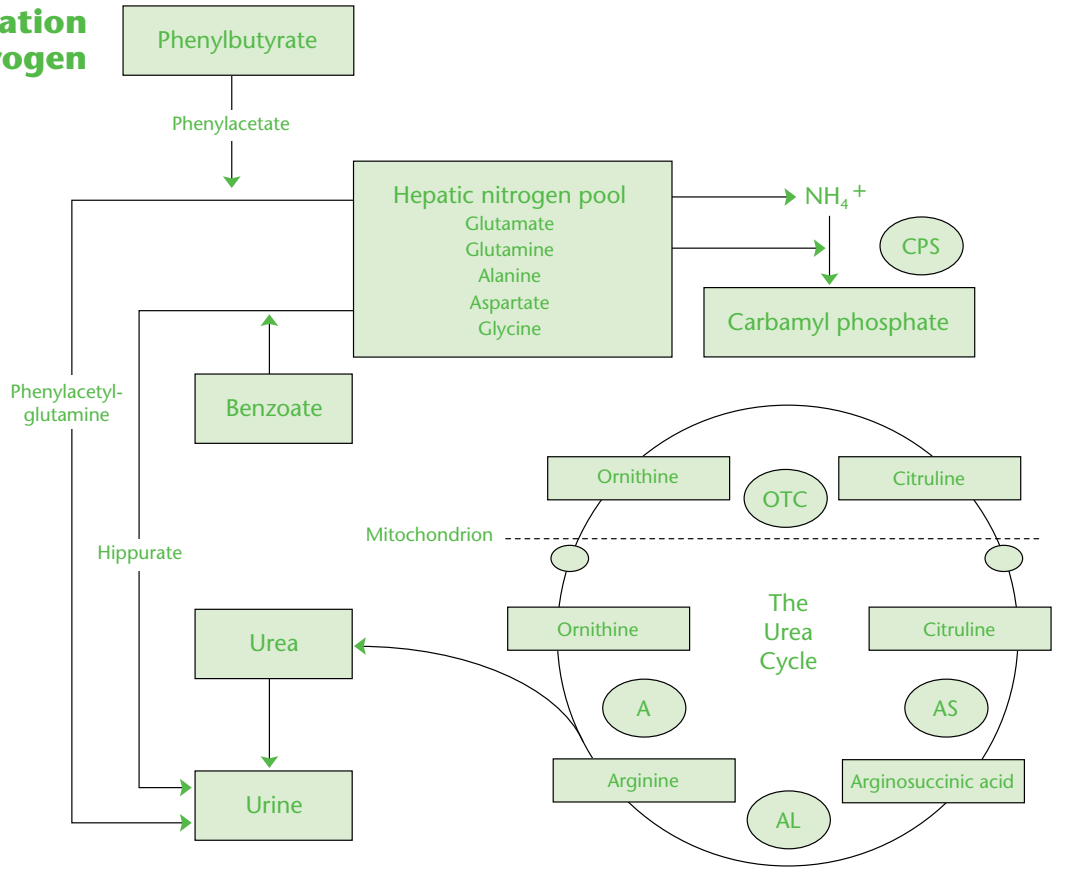
Emergency treatment of urea cycle disorders (UCDs) during acute decompensation is the same for all enzyme deficiencies (except arginase deficiency where arginine supplement is not required). It involves:

- **withdrawal of dietary nitrogen except arginine which is often given via intravenous infusion if the oral route is unavailable due to vomiting**
- **provision of an alternative energy source, such as glucose, to suppress endogenous energy protein catabolism†**
- **elimination of nitrogenous waste via alternative pathways by using sodium benzoate and sodium phenylbutyrate (see the figure overleaf) via intravenous infusion. Carglumic acid is a very effective treatment for the acute management of hyperammonaemia**

Emergency treatment requires frequent monitoring of plasma ammonia to ensure treatment response.

Carglumic acid (Carbaglu®) is a recently licensed product used in the treatment of hyperammonaemia associated with N-acetyl glutamate synthetase (NAGS) deficiency. It is an analogue of N-acetyl glutamate that stimulates carbamyl phosphate synthetase to incorporate ammonia into the urea cycle.

Elimination of nitrogen



CPS= carbamyl phosphate synthetase
OTC = ornithine transcarbamylase
A = arginase
AL = arginosuccinate lyase
AS = arginosuccinate synthetase

Alternative pathways

Maintenance treatment involves a protein-restricted diet, supplemented with arginine and high calorie feeds. The exception to this is in arginase deficiency. Arginase is the enzyme which converts arginine into urea for elimination from the body. High concentrations of arginine are thought to contribute to the neurological damage seen in patients with arginase deficiency. It is important therefore not to give arginine supplementation to these children.

Activity 12.4

List the five enzymes involved in the urea cycle.

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